PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference NP0012	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/EP2004/051550	International filing date *(day/month/year)* 20.07.2004	Priority date *(day/month/year)* 31.07.2003
International Patent Classification (IPC) or national classification and IPC A61K31/4178, A61K31/4184, A61K31/41, C07D403/10, C07D257/04, C07D403/04, C07D409/06		
Applicant NICOX S.A.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.01.2005	01.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Cortés, J Telephone No. +49 89 2399-8206

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/051550

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-68 as originally filed

   Claims, Numbers

   1-14 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents have been cited in the International Search Report:

D1: WO 00/61537 A (NICOX SA (FR)) 19 October 2000 (2000-10-19)

D2: WO 03/013499 A (NICOX SA (FR)) 20 February 2003 (2003-02-20)

D3: MCINTYRE ET AL.: "Losartan, an Orally Active Angiotensin (AT1) Receptor Antagonist: A Review of Its Efficacy and Safety in Essential Hypertension" PHARMACOL. THER., vol. 74, no. 2, 1997, pages 181-194, XP002262197

D4: EP-A-0 955 294 (SMITHKLINE BEECHAM CORP (UK)) 10 November 1999 (1999-11-10)

D5: HEDNER T ET AL: "A COMPARISON OF THE ANGIOTENSIN II ANTAGONISTS VALSARTAN AND LOSARTAN IN THE TREATMENT OF ESSENTIAL HYPERTENSION" AMERICAN JOURNAL OF HYPERTENSION, NEW YORK, NY, US, vol. 12, no. 4, April 1999 (1999-04), pages 414-417, XP000866169

D6: EP-A-1 312 379 (TAKEDA CHEMICAL INDUSTRIES LTD (JP)) 21 May 2003 (2003-05-21)

D7: "TELMISARTAN" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 22, no. 10, 1997, pages 1112-1116, XP009008343 ISSN: 0377-8282

D8: "OLMESARTAN MEDOXOMIL CS-866 BENEVAS ANTIHYPERTENSIVE ANGIOTENSIN AT ANTAGONIST" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 25, no. 11, November 2000 (2000-11), pages 1217-1218, XP009030725 ISSN: 0377-8282

D9: HEDNER T: "THE CLINICAL PROFILE OF THE ANGIOTENSIN II RECEPTOR

BLOCKER EPROSARTAN" JOURNAL OF HYPERTENSION, CURRENT SCIENCE, PHILADELPHIA, PA, US, vol. 20, no. SUPPL 5, 2002, pages S33-S38, XP008011504 ISSN: 0263-6352

Novelty (Article 33(2) PCT)

The present invention is a novel selection of D1. The distinctive feature is the choice of the specific positions at which the group -Y-O-NO_2 is attached to the drug residue (i.e the specific positions of the group N_0).

The present compounds differ from D2 in that the drug residue is an angiotensin inhibitor and from the compound in D3 in that the active drug residue is not derivatized with the group -Y-O-NO_2.

The present invention is therefore novel.

Inventive Step (Article 33(3) PCT)

D1 generically discloses nitrooxy derivatives of anti-angiotensin drugs and mentions specifically the angiotensin receptor inhibitor losartan (D1: e.g. 2nd paragraph, page 6 and formula (I), page 7). D1 further discloses a nitrooxy-derivative of the ACE-inhibitor enalapril (D1: example 12) and discloses experimental data showing that nitrooxy derivatives of active drug substances have a blood pressure lowering activity when compared to the respective underivatized drug compounds (D1: e.g. table VI, page 126). D1 teaches generally that nitrooxy-derivatives of ACE-inhibitors have a better therapeutic efficacy and lower side effects (D1: e.g. 1st paragraph, page 38).

D1 can be regarded as the closest prior art.

D2 discloses nitrooxy derivatives of biphenyl-based drugs such as flurbiprofen for the treatment of cardiovascular diseases (e.g. compound (V)). D3 discloses the active principle losartan and its pharmacology.

D4 discloses imidazole-nitro derivatives as angiotensin II receptor antagonists but no nitrooxy-derivatives.

D5 to D9 disclose the active principles valsartan, candesartan, telmisartan, olmesartan and eprosartan, respectively, as well as their pharmacology (angiotensin II receptor inhibitors).

The problem of the invention was the provision of new angiotensin II receptor antagonists with improved pharmacological properties.

The experimental data in the present description show an improved inhibition of the vasorelaxant activity, an improved inhibition of the LPS-induced nitrite accumulation (improved antiinflammatory activity), an improved inhibition of platelet aggregation as well as an improved antihypertensive activity (see tables 1-4 in the present description).

The combination of the first three pharmacological effects is suprising and could not be anticipated from D1 or from any other of the cited documents.

The present application is therefore based on an inventive step.